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Oncology

Is Trioxide Arsenic Useful for the Treatment of Acute Myeloid Non-promylocytic Leukaemia?

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ABSTRACT

Introduction: Acute leukaemia has a severe clinical process and can be rapidly fatal if it is not treated. Despite the modern treatment, many patients die due to the nature of the disease or the treatment side effects. Among the proposed forms of treatment, there is no standard and uniform treatment for those who are not completely remitted or those who had a reactivation of the disease. Therefore, it is emphasis to a newer treatment as a medical emergency. With due attention to the toxicity of the cytotoxic drugs, a series of non-toxic treatment options have been proposed. One of the newer drugs which are used for the treatment of acute leukaemia is Trioxide Arsenic. Because of the appropriate response of acute promylocytic leukaemia (APL) to Trioxide Arsenic and because of its relatively lower side effects, we decided to use it for the treatment of acute myeloid leukaemia (non-promylocytic) (AML) which was resistant to drug therapy.

Aim of the Study: We aimed to assess the complete remission with Trioxide Arsenic in patients with acute myeloid leukaemia (non-promylocytic) who were resistant to therapy and its correlation with the age and duration of the disease from the diagnosis to the treatment.

Material and Method: Patients with acute myeloid leukaemia, who were resistant to the treatment, were enrolled in the study. A complete history was obtained and a complete physical examination was done before the treatment. Peripheral blood smear and bone marrow examinations were done during the therapy, every two weeks. The treatment with Trioxide Arsenic was started. The complete remission was confirmed according to the standard definition of remission for acute myelogenic leukaemia.

Results: In our study, out of 7 patients, one had complete remission, one had partial remission and 4 patients had no remissions. One patient abandoned the study. There was no significant correlation between the times of the treatment, from the beginning of the disease until the beginning of the treatment. Also, there was no significant correlation between the age of the patients and their response to Trioxide Arsenic. The median survival for the patients was 3.66 months and all the patients who responded and did not respond to the treatment, died.

Conclusion: According to the median survival of the patients, it seems that Trioxide Arsenic alone is not a good drug for the treatment of acute myeloid non-promylocytic leukaemia. However, with regards to one complete remission and one partial remission and the lesser side effects of Trioxide Arsenic, we recommend the use of this drug in clinical trials and in the lab cultures of the leukaemic cells.

Key Words: Trioxid Arsenic, Promylocytic myeloid leukaemia, Acute non-promylocytic myeloid leukaemia

INTRODUCTION

Acute myeloid leukaemia is an infiltration of haematopoietic neoblastic cells which are derived from myeloid cells in the blood, bone marrow and other tissues of the human body. Acute leukaemia has a rapid clinical course and if it is not treated medically, it can be severely fatal [1]. Acute myeloid leukaemia (AML) is usually seen in elderly people. The mean age is 65 years and if it is not treated, the median survival period is less than 3 months [2]. Despite innovative treatment, the patients die, either due to the disease or due to the complications of the treatment [3] 60-80% of the younger patients were found to attain a complete remission following the recent, standard, aggressive and maintenance treatment, but however, this percentage is lower in adults [4, 5]. The current treatment for AML is the 7+3 regimen which includes Citarabine and Anthracycline. Anyway, this type of therapy does not cure many patients. Relapse was seen in 50% of the patients who were in complete remission. Consequently, despite the treatment, the 2 year survival in the patients with the reactivation of the disease was only 20%. Among the proposed treatments, there is no uniform standard treatment for the patients who have the reactivation of the disease [6-8].

So, if the patient dose not respond to two consecutive aggressive therapies, the outcome will be poor and furthermore, the treatment regimen will be more complicated. For this reason, an approach to a newer therapy is a medical emergency.

Due to the toxicity of the cytotoxic drugs, a series of non-toxic treatments are on the way,which include differentiating agents, enzyme inhibitors and monoclonal antibodies [8]. One of the new drugs is *Trioxide Arsenic*. This drug has the ability to cause differentiation and apoptosis in the promylocytic leukaemic cells. Complete remission with this drug was seen in 85% of the patients who were affected by promylocytic leukaemia in its relapse. Recently, this drug has been used to treat other forms of acute promylocytic leukaemia [9-11]. With regards to a complex of these investigations and the relatively lesser side effects of Trioxide Arsenic, we decided to use it for the treatment of acute myeloid leukaemia (non-promyelocytic), which was resistant to the treatment [12].

MATERIAL AND METHOD

For 3 years (from to), the patients with acute myeloid leukaemia who were resistant to the treatment, who were referred to our clinic, were enrolled in an analytical, cross-sectional study. A written consent for the treatment trials was obtained from all the patients. Before the treatment, a complete history was obtained

and careful physical examination was done. Also, the time which elapsed from the beginning of the disease and the start of the treatment with Trioxide Arsenic was recorded. The CBC count was obtained, staining of the slides with Peroxidase was done and the levels of creatinine, urea, fasting blood sugar, transaminase and electrolytes including Na, K and Mn were evaluated The ECG was also recorded. During the treatment, the bone marrow examination and PBS were done every week. The ECG was checked and the above mentioned laboratory tests were done 3 times a week. The treatment with Trioxide Arsenic was started with a dose of 0.1 mg/kg daily by IV infusion for 2 hours. During the therapy, if the patients reached complete remission, the treatment would be continued for another week; otherwise, the treatment was continued for up to 56 days. The complete remission was based on the standard characteristics of the complete remission for acute myelogenic leukaemias.

RESULTS

A total of 7 patients with AML and non-APL were referred and treated by Trioxide Arsenic. The demographic and other data of the patients are listed in [Table/Fig-1]. One patient (14.3%) discontinued the drug ten days after the beginning of the treatment. One patient (14.3%) had complete remission, but died due to an acute crisis after the treatment. One patient (14.3%) had partial remission (blasts less than 20%), but died due to acute leukaemia. Four patients (57.1%) did not respond to the therapy and all of them died due to the complications of leukaemia. Overall, 6 patients underwent the treatment; 1 patient had a partial response,1 had a complete response (both 28.6%) and 4 patients did not respond to the treatment [Table/Fig-2].

Results	Duration of Treatment	Time elapsed from diagnosis to treatment (Month)	Age of the patient	Patient
No response	+51	7	16	1
Stop treatment	+10	3	55	2
Remission, reactivation, death	+56	3	51	3
no response, death	+47	4	56	4
Partial remission	+39	11	47	5
No remission, death	+40	35	68	6
No remission, death	+20	1	71	7

[Table/Fig-1]: Patient's age, Time elapsed from diagnosis to treatment, Duration and results of treatment

Results	Percent	No	Cumulative percent
Non responded	57.1	4	57.1
Recovery	28.6	2	85.7
Drop from study	14.3	1	100.0
Total	100.0	7	

[Table/Fig-2]: Result of the study

The mean time from the diagnosis to the treatment with Trioxide Arsenic was 5.14 ±1.18 months for all the patients, it was 4.75±1.1 months for the patients who did not respond to the treatment and it was 7±4 months for the patients who completely or partially responded to the treatment [Table/Fig-3]. This difference was not statistically significant. The mean age of the patients was 52± 1.1 years. The mean age was 52.75±12.67 years for the patients who did not respond to the treatment and it was 49±2 years for the patients who responded completely or partially to the treatment [Table/Fig-3]. This difference was not statistically significant. The mean time of the treatment with Trioxide Arsenic was 40± 6.87 days. This period was 39.5±6.88 days for those who did not respond to the treatment and it was 56 days in the patients who responded completely or partially to the treatment [Table/Fig-4]. This difference was not statistically significant.

The median survival time after the start of the treatment was 3.66 months. All the patients died as a result of leukaemia, but not due to the alterations in the laboratory tests which included creatinine, urea, FBS, transaminase, K, Na, Mg which They died due to the side effects of the therapy. We did the CBC count of all patients during the treatment. The patients who had complete or partial remission did not need any therapy for anaemia and thrombocytopaenia. Patients who did not respond to the treatment had CBC changes which were related to leukaemia, which needed treatment. There were no ECG changes in any patients.

DISCUSSION

Over the last few decades, a variety of clinical researches which were conducted worldwide, have demonstrated the efficacy of Trioxide Arsenic for treating relapsed acute promyelocytic leukaemia. Currently, the role of this drug in the front-line therapy is under investigation [13]. Recent trials have demonstrated that its addition to the standard treatment regimens could improve the patients' survival and outcomes and that it might allow a reduction in the cytotoxic effects of the drugs. It has also been revealed that the therapeutic doses of Trioxide Arsenic are well tolerated, with no evidence of long-term toxicity. The adverse events include electrocardiographic abnormalities and mild elevations in the liver enzymes. But, these side effects were found to rarely occur [14].

In our study on 7 patients, one of them was found to have complete remission, one had partial remission and four of them showed no response to the treatment. One patient left the study. There was no statistically significant correlation between the period of the time between the diagnosis and the start of the treatment with Trioxide Arsenic and also between the age of the patients and their response to Trioxide Arsenic.

	Response of Treatment	Number	Mean	Std. Deviation	Std. Error Mean
Age (Year)	No Response	4	52.7500	25.34265	12.77133
	Partial or Complete	2	49.0000	2.82843	2.0000
Start of Treatment (Month)	No Response	4	4.7500	2.21736	1.10868
	Partial or Complete	2	7.0000	5.65685	4.0000
Duration of Treatment (Day)	No Response	4	39.5000	13.77195	6.88598
	Partial or Complete	2	56.0000	0.0000	0.0000

[Table/Fig-3]: Mean of Age, Start of Treatment and Duration of Treatment with Complete or Partial Remission or without response to treatment

The mean survival of our patients was 3.66 months, but it was found that if the patients were not treated, their mean survival was less than 3 months. Due to a low sample size, we couldn't confirm these findings. For a better conclusion on the effect of Trioxide Arsenic on the mean survival; more detailed investigations with more numbers of patients are needed.

In their study, Simrit Parmar et al reported that of 11 patients who were affected by AML and non APL, none of them responded to the treatment with Trioxide Arsenic and that the disease progressed in all patients [15]. The mean survival of these patients was 2.25 months as compared to the 3.66 month survival in our patients. The difference between these 2 groups may be the number of patients in both the groups. Our patients were treated with first line treatments and salvage protocols, but in the Simirit Parmar study, the patients were those in whom the disease had relapsed and those who had failed to respond to the first line treatment, those who had secondary AML or whose age was more than 65 years old. Maybe their genetic and racial backgrounds had an influence on their treatment. Although the dose of Trioxide Arsenic in their study was higher than that in our study, no results were obtained. However, to confirm the effect of Trioxide Arsenic in the treatment of AMLand non-APL, a study with a large sample size is needed We concluded that ATO should not be used (at least) alone, for patients with AML and non APL. However, in our study, one case had complete remission after using Trioxide Arsenic alone.

Safak Yuske et al observed that high doses of methyl prednisolone caused the differentiation of the myeloid blast cells into mature granulocytes . If methyl prednisolone was given with ATO, it would also result in the differentiation of the acute myeloid leukaemic cells and thus, these drugs would have a synergic effect [16]. In our study, ATO was given alone. With regards to the synergic effect of Trioxide Arsenic and methyl prednisolone, these drugs should be used together in future.

Gail et al studied patients with AML and non-APL, who were over 60 years old. These patients received Trioxide Arsenic plus low dose Citarabine. Out of the 61 patients, 21 attained complete remission (34%). This study concluded that adding ATO to low dose Citarabine was better than using Citarabine alone. So, it seemed that low dose Citarabine and Trioxide Arsenic together had a synergic effect [17]. We used ATO alone; out of 7 patients, only one patient (14.3%) had complete remission. Our study has no age limitation, but in Gail et al's study the patients who were selected were more than 65 years old. Did the age factor in these two studies have an effect on the treatment outcome or not? This is a question that needs to be answered through future studies.

Another study showed that if the catalizator which was used on the leukaemic cells was accompanied by ATO, it would result in a higher mortality rate of the cells in comparison to the use of ATO alone. Also, adding FLT3 inhibitors to the Trioxide Arsenic increased the inhibition of the growth and apoptosis of the myeloid leukaemic cells in comparison to the use of ATO alone. Also, in a study on rats with AML and non APL, it was seen that the inhibition of compensating increased Gluthatione could decrease the resistance to Trioxide Arsenic and that it consequently increased its cytotoxicity effect. In our study, we used ATO alone. Perhaps, if the inhibitors of catalase, FLT3 and compensating increased of glutathione were used accompanied with Trioxide Arsenic; we have better response in our patients. Aquaglyceropurine (AQP) could play a role in the intracellular absorption of Arsenic and so, an increase in the dose of Aquaglyceropurine could increase the cytotoxicity of ATO. The use of ATRA could increase the Aquaglyceropurine 9. Thus, the synergic effect of ATRA and ATO is due to this mechanism. Therefore, the use of ATRA with ATO could increase the expression of Aquaglyceropurine 9 and this could improve our results [18-20].

CONCLUSION

Although in our study, one of the 7 patients had complete remission, because of the short mean survival of the patients, it seems that Trioxide Arsenic alone is not a suitable drug for patients with AML and non APL. However, with due attention to this fact that we had one complete remission and one partial remission and also because of the lesser side effects of Trioxide Arsenic, it was not wise to put it off. Therefore, it is necessary that this drug be used in the first phase of the clinical trials and for the cell cultivation of leukaemia samples in the laboratory.

From the investigations which were made on the cell cultivation media, on laboratory animals and in aged patients and in the first phase of the clinical trials, it was seen that the use of a high dose of methyl prednisolone, a low dose of citarabin, inhibitors of catalase, inhibitors of FLT3 and inhibitors of compensating increased of gluthatione resulted in an increased effect of Trioxide Arsenic. Therefore, it recommended that the use of these drugs be accompanied by the use of Trioxide Arsenic, which was assessed in clinical trials and in the laboratory cell cultivation of the leukaemic cells.

Knowledge about the real mechanism of action of Trioxide Arsenic can give us better information about the dose of the drug, the factors which influence the increase and decrease of its action and the factors which have a synergic effect with Trioxide Arsenic. Therefore, there is a need for more studies in this area.

Finding new methods of treatment, especially non toxic drugs for patients with acute myeloid leukaemia, should be considered as a medical emergency and it should be a part of all the research programs.

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